

Asthma and the Environment

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In the United States and many other countries, the prevalence of asthma in both adults and children is rising, an increase that cannot be reconciled simply by changes in diagnostic categorization. The increase in prevalence is too rapid to be explained by alterations in the gene pool and is thus a growing interest in the environment and asthma. Data from the second National Health and Nutrition Examination Survey (NHANES II) indicate that in 1987 there were approximately 25 million individuals in the United States who currently or previously had asthma or symptoms associated with asthma. Illness associated with asthma accounts for an estimated 27 million patient visits and 470,000 hospital admissions annually; this translates into an estimated loss of 3 million workdays and 90 million days of restricted activity. Asthma is more prevalent among 6 to 11-year-old black children than among white children at the same age, and an even higher prevalence is noted among children of Puerto Rican descent. Although asthma deaths are infrequent, mortality rates have increased 66% since 1980. The costs related to this disease are enormous, with an estimated cost in the United States in 1990 of \$6.2 billion.

There is mounting evidence that air pollutants are involved in exacerbating asthma. Controlled laboratory exposure studies show that specific air pollutants stimulate bronchoconstriction or airway inflammation. The U.S. Clean Air Act of 1970 provides special consideration to criteria air pollutants including O₃, SO₂, particulate matter <10 µm (PM₁₀), NO_x, and Pb. National Ambient Air Quality Standards for these pollutants are set by the U.S. Environmental Protection Agency (EPA), with particular concern for populations at risk. Asthmatics are more sensitive to several of these pollutants and therefore constitute a susceptible population. The EPA has considerable interest in asthma as a public health and an environmental health issue.

Workshop Goals and Structure

The EPA and several other public health agencies jointly sponsored a workshop 7–9 May 1996, in Chapel Hill, North Carolina, to discuss the possible links between environmental pollutants and asthma. The workshop's objective was to review recent findings pointing to an association between environmental pollutants and asthma. In addition,

the workshop provided a platform to discuss recent advances and identified major scientific uncertainties that limited risk assessment. In keeping with these objectives, the EPA specifically needs to determine the extent to which asthmatics represent a high risk population for air pollutants and characterize the nature of the risk, which includes dose–response assessments, risk factors, and mechanistic information.

The structure of the workshop included four scientific sessions with five to eight plenary speakers and one or two co-chairmen (see list). At the end of each session, a panel of experts addressed specific questions facilitated by a rapporteur (see list). The workshop brought together basic scientists, clinicians, and epidemiologists from academia and various public health agencies, all of whom share an interest in asthma and the environment.

Session I: The Asthma Phenomenon

This session set the stage for the workshop, and provided everyone with the big picture. Worldwide demography and changes over the past quarter-century were reviewed. Asthma is an increasingly prevalent diagnosis, especially among children in affluent countries that have become heavily urbanized. Australasia has an exceptionally high prevalence for as yet unknown reasons. Chinese Americans in Hawaii have a very low prevalence compared to other ethnic Hawaiian groups. In the continental United States, asthma prevalence is increasing among black children, particularly in certain areas of New York and Chicago. This trend is consistent with an effect of urbanization, but not with increasing affluence.

Risk factors for the development of asthma include both a genetic base and environmental triggers such as postnatal exposure to maternal cigarette smoke. Ambient air pollutants may cause nonspecific airway reactivity and inflammation, provoke acute bronchospasm, and enhance the response of allergic asthmatics to specific antigen challenge. The extensive epidemiology linking ambient air pollution—especially involving ozone and particulate matter—with asthma exacerbations was emphasized. Indoor air contaminants associated with asthma include indoor antigens (e.g., housedust mite, cat, cockroach), biologicals such as endotoxin, and various

gases and particles of nonbiological origin.

The general immunologic mechanisms in asthma and the specific role of the CD4⁺-T lymphocyte of the T_H2 category were reviewed. Viral upper respiratory tract infections were noted to play an important role in asthma exacerbations. In addition, acute viral infections may be critical events in the initial development of the asthmatic state. If inhaled pollutants interact with respiratory epithelium to enhance susceptibility to viral infection, this might indirectly influence asthma pathogenesis and exacerbations. Finally, in considering air pollution–asthma interactions, the role of the epithelial lining of the airways was considered; this is the primary target of inhaled reactive pollutants, which interact with submucosal cellular and vascular elements through epithelial cytokines and chemokines, neural pathways, and perhaps mediators like nitric oxide.

Session II: Environmental Epidemiology

This session reviewed the most recent epidemiology studies linking environmental pollutants and asthma. Although there is considerable evidence that ambient air pollution can exacerbate asthma, aggregate data on temporal changes in asthma prevalence do not support a relationship between the initiation of asthma cases and ambient air pollutants. Despite a monotonic increase in asthma deaths in the United States between 1979 and 1989, ambient concentrations of particulates and sulfur oxides have steadily declined. Furthermore, asthma mortality does not appear related to differences in air pollution concentrations across cities.

The issue of wheezing before age 6 was examined as a risk factor for childhood asthma. Results from studies in Arizona suggest that there are two types of wheezing

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illnesses occurring before age 3. One form is more common, has a good prognosis, and is associated with lower levels of lung function at birth. The second, a more persistent form, is associated with normal levels of lung function at birth but diminished lung function at age 6. Children with this form have many of the risk factors that are associated with asthma later in life (family history of asthma, personal history of allergic disease, high IgE levels, etc.).

The effects of long-term residence in communities with high ambient ozone levels on the risk of developing asthma have been studied among Seventh Day Adventists in California. For participants free of asthma in 1977, the 15-year cumulative incidence of doctor-diagnosed asthma was 2.8 and 3.6% in males and females, respectively, and was related to 8-hr ambient ozone concentration for males, but not for females. Among males who had doctor-diagnosed asthma but no symptoms in 1977, the development of new asthma symptoms was related to ozone concentration.

The difficulties in showing convincingly that long-term exposure to ambient particulates causes asthma is in part related to absence of control for environmental allergens from dust mites, pets, and pollen. Nevertheless, a number of studies show positive associations of ambient particulate levels with hospital admissions for asthma and with acute symptoms, bronchodilator use, and lung function in panels of asthmatics. A positive association between the self-reported frequency of truck traffic, but not automobile traffic, was reported near the residence of study subjects in two German cities, Bochum and Münster. The prevalence odds ratio for the association of wheezing and frequent truck traffic was 1.5–1.6, and for symptoms of allergic rhinitis was 1.7–2.0. There was no indication of confounding by smoking, pets, or markers of socioeconomic status. Because misclassification resulting from self-reports of traffic exposure cannot be ruled out, there is a need for further investigation using more refined measures of exposure.

Work funded by the National Institute of Allergy and Infectious Diseases through the National Cooperative Inner City Asthma Study was described. These studies focus on minority populations, with objectives to identify risk factors and effective interventions that are culturally appropriate and geared toward self-management. The health outcomes include hospital and emergency room visits and absences from school or work. The National Institute for Occupational Health and Safety provided an overview of occupational asthma research and surveillance at the Institute. The

National Institute of Environmental Health Sciences proposed the work "Environmental Interventions in the Primary Prevention of Asthma in Children." Five hundred infants from lower socioeconomic families with an asthma history will be randomized at birth into intervention and control groups and assessed for asthma symptoms. Environmental interventions to protect infants from exposure to mite and cockroach allergens will be implemented. Overall, these presentations point to a need for expanded research into environmental factors associated with the induction of asthma, particularly among infants and young children.

Session III: Controlled Exposure Studies

This session focused on the role of acute exposure to specific environmental pollutants in the asthmatic response and addressed the following questions: Does ozone sensitize asthmatic airways and increase susceptibility to a subsequent allergen challenge? Is the inflammatory response of asthmatics to ozone different from normal individuals? Do moderate asthmatics respond differently to ozone than mild asthmatics? Are animal models instructive in understanding the response of asthmatics to pollutants?

Exposures to ozone under controlled conditions have demonstrated similar sensitivity for asthmatic and normal subjects, at least as measured by lung function symptoms. However, mechanisms unrelated to direct ozone-induced bronchoconstriction could enhance sensitivity of asthmatics. Recently, it was reported that inhalation of 0.1 ppm ozone sensitized asthmatic airways, making them more susceptible to a subsequent challenge with allergen. Two presentations further examined the ozone-allergen interaction. One group was unable to confirm increased responsiveness to allergen in asthmatics exposed to 0.2 ppm ozone for 1 hr, with intermittent exercise. These findings support recent studies for mild asthmatics exposed to 0.1 ppm ozone for 1 hr at rest, but contrast with other investigators who observed increased bronchial responsiveness in asthmatics exposed to 0.25 ppm ozone for 3 hr with moderate exercise. The interaction between ozone and allergen in asthmatics has also been assessed using nasal lavage. Mild resting asthmatics exposed to 0.4 ppm ozone required less allergen instilled into the nose to elicit symptoms. Thus, there are suggestions that prior ozone exposure sensitizes the nose or airways to a subsequent allergen challenge, but further work is needed.

Subsequent presentations focused on direct effects of ozone on the induction of inflammatory mediators in asthmatics.

Ozone-induced changes in bronchoalveolar lavage (BAL) protein levels were similar between normal and asthmatic subjects, but asthmatics had a more pronounced polymorphonuclear neutrophils (PMN) influx. This agrees with the data using nasal lavage in which higher numbers of PMNs, as well as eosinophils, in asthmatics exposed to ozone were compared with normal subjects. Mild asthmatics exposed to 0.2 ppm ozone for 4 hr with intermittent moderate exercise had increased BAL levels of PMNs, eosinophils, and lymphocytes. Additional data showed increased numbers of eosinophils and eosinophil cationic protein (ECP) in nasal lavage fluid of asthmatics exposed to ozone. These studies suggest that asthmatics may respond to ozone with an influx of eosinophils. Furthermore, it was observed that moderate asthmatics exposed to 0.16 ppm ozone for 7.6 hr had more symptoms and greater decrements in forced expiratory volume in 1 sec (FEV₁) and FEV₁/forced vital capacity than normal subjects. Asthmatics requiring inhaled beta agonists during the exposure had even greater decrements in lung function. Future work with more significantly obstructed asthmatics may help resolve the discrepancy between epidemiology, suggesting that asthmatics are more sensitive to ozone, and findings from controlled exposure studies. The clinical data, nevertheless, provide compelling evidence that ozone exposure directly induces substantial bronchoconstriction in moderate asthmatics.

Animal models are potentially useful for studying biological mechanisms responsible for the sensitization phase of asthma. It was demonstrated that immediate hypersensitivity responses in allergic rats were associated with high titers of IgE antibody in serum, but that immune-mediated inflammation and airway hyperresponsiveness were independent of reaginic antibody levels. Intriguing data were presented indicating that these latter clinical features of asthma could be transferred to recipient animals by injection of lymphocytes. Pretreatment with IL-12 appeared to block allergic inflammation by increasing T_H1 cytokines (interferon γ and TNF α) in BAL fluid of mice. Finally, exposure to 5 ppm NO₂ after sensitization and antigen challenge up regulated lymphocyte function, allergen-specific antibody levels, and immune mediated pulmonary function in the lung.

Session IV: Mechanisms of Response in Asthma

The primary focus of the presentations in the last session was to explore the mechanisms and factors involved in the exacerbation and persistence of asthma.

The complex cellular and molecular processes that contribute to airway inflammation were reviewed; it was emphasized that they are interactive, redundant, and self-perpetuating—a recurrent theme in this session. The important role of cytokines in the initiation and resolution of the inflammatory response was emphasized. New data suggest that cytokines are encrypted and presented with local, site-specific actions. The local cytokine milieu includes several cytokines produced from different cells or varying ratios of cytokines produced by a single cell type. For example, when T_H2 cells are challenged with increasing concentrations of antigen, the ratio of release of two cytokines (IL-4: interferon γ) will change from a T_H2 through a T_H0 to a T_H1 profile as the concentration of antigen increases.

The pathologic processes in asthma have been recognized to include dysregulation of inflammation and injury processes. New work is now pointing to dysregulation of cell death and cell repair processes. For example, data obtained from *in vitro* studies indicated that altered apoptosis is present in subjects with peripheral eosinophilia.

Respiratory viral infections (rhinovirus and respiratory syncytial virus) and their role in the exacerbation of asthma were discussed. Experimental rhinovirus infection can be performed in controlled human challenge settings and *in vitro* and the virus assayed via polymerase chain reaction in nasal secretions, lavage fluid, and biopsy samples. Rhinovirus infection causes few cytopathologic changes, but induces an immune response that up regulates preexisting inflammation in the asthmatic airway. Rhinoviruses bind to the ICAM-1 receptor of the epithelial cell, a receptor whose expression may be altered by pollutant exposure. Rhinovirus increases ICAM expression and potentiates histamine release and eosinophil recruitment. Cytokines detected in nasal aspirates following rhinovirus infection include TNF α , IL-11, interferon- γ , IL-1 α , and chemokines IL-8, RANTES, and MIP1 α . Rhinovirus infection can induce prolonged increases in airway hyperreactivity and induce a late response to the antigen.

Environmental factors alter the composition and fate of aeroallergens. Interesting data were presented indicating that the bioavailability of grass antigen in pollen grains can be markedly altered by increased humidity, sulfate exposure, and NO₂ exposure. Pollen may complex with ambient particulate pollution, thus altering the exposure characteristics and possibly the biological response to these agents.

General discussion returned to the two fundamental questions. First, do environmental pollutants cause asthma? Although

Workshop speakers	
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David V. Bates University of British Columbia	Hillel S. Koren U.S. Environmental Protection Agency
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Kurt Blaser Swiss Institute for Allergy and Asthma Research	William F. McDonnell U.S. Environmental Protection Agency
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Douglas W. Dockery Harvard School of Public Health	Edward L. Petsonk National Institute for Occupational Safety and Health
Peyton A. Eggleston Johns Hopkins University	Lawrence W. Reiter U.S. Environmental Protection Agency
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participants recognized that the causes of asthma are unknown, ecological comparison (e.g., Northern vs. Southern Hemisphere; East vs. West Germany studies) demonstrates regional differences in atopic sensitization and asthma implicating environmental factors in the broadest sense. Unfortunately, only limited data address the role of air pollution in the initiation of asthma. Nevertheless, epidemiologic findings have identified a possible role for ozone in adult-onset asthma, but only in males. Second, can environmental pollutants exacerbate asthma? In general, it was felt that the more robust data sets indicate that photochemical air pollution (including ozone) can exacerbate asthma. The potential mechanisms of ozone-induced exacerbations were enumerated and included altered viral infectivity (e.g., through up regulation of the ICAM-1 rhinovirus receptor) and shifting the baseline or antigen-induced cytokine profile.

Summary of Research Recommendations

The group was unanimous in recommending a broad-based approach to studying

asthma and the environment. Basic immunologic, genetic, molecular, and cellular studies, epidemiologic investigation, animal models, and controlled human exposures are all important parts of the research armamentarium. There was agreement that environmental factors may be exacerbating asthma, although inadequate data for linking air pollution exposure in the initiation of asthma exist (except in occupational settings).

Therefore, it is recommended that research into environmental factors associated with the initiation of asthma, particularly among infants and young children, should be expanded. While the evidence that ambient air pollutants and other environmental factors can exacerbate asthma is reasonably strong, the role of these factors in inducing the asthmatic state is unknown. The role of viruses, cigarette smoke, and allergens in both young children and adults should be emphasized, in order to understand their contribution to the inflammatory response of epithelium and the cytokines generated. Epidemiologic investigations should address incidence and consequences of viral respira-

Workshop chairs and rapporteurs**The Asthma Phenomenon**

Lawrence W. Folinsbee, U.S. Environmental Protection Agency
Philip A. Bromberg, University of North Carolina at Chapel Hill

Environmental Epidemiology of Asthma

Fred Henderson, University of North Carolina at Chapel Hill
Carl M. Shy, University of North Carolina at Chapel Hill

Controlled Exposure Studies

Howard Kehrl, U.S. Environmental Protection Agency
Daniel Costa, U.S. Environmental Protection Agency
Robert Devlin, U.S. Environmental Protection Agency

Mechanisms of Response of Asthma

Hillel S. Koren, U.S. Environmental Protection Agency
Rebecca Bascom, University of Maryland School of Medicine

Workshop Summation

Mark J. Utell, University of Rochester Medical Center

tory infections during high levels of pollutants, as well as interactions of allergens and viruses in causing and exacerbating asthma.

Animal models are now available for studying biological mechanisms responsible

for the sensitization phase of asthma. The potential role of "knock-out" animals in better understanding contributions of environmental pollutants should be valuable. Additional work is needed to determine the

genetic markers of individuals at risk for developing pollutant-related effects.

More information is needed on the dosimetry of gaseous and particulate-matter pollutants in asthmatics. While the dosimetry is reasonably well understood in the normal lung, there is much less information available in mild to severe asthmatics. This may be of considerable importance in establishing a mechanism to explain this association of particulate matter and asthma exacerbations and hospitalizations.

Finally, the opportunity now exists to study injury and repair in asthma at the cellular and molecular level. The role of airway injury in maintaining persistent asthma is unknown. In addition, whereas airway inflammation is known to be associated with airway hyperreactivity, the link with faulty epithelial repair with persistent asthma has not been made. It was felt that many of these issues could be addressed in animal models and eventually extended to human studies.

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